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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/954,771	10/20/1997	PHILIP W. INGHAM	HMSU-P11-006	6520

28120 7590 02/25/2003

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EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 02/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/954,771	Ingham, PW
Examiner	**Art Unit**
Michael Brannock	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 15, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *123-166* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *123-166* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Detailed Action

Status of Application: Claims and Amendments

1. The request filed on 11/15/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08954771 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 123-166 are pending.

3. Applicant is notified that the amendments put forth in Paper 45, 12/4/02, have been entered in full.

4. Claims 123-166 are provisionally rejected under the judicially created doctrine of double patenting over claims 11-13 of copending Application No. 08/462386. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: *in vitro* methods of promoting the growth, differentiation and/or survival of neuronal cells by contacting the cells with a sonic hedgehog protein.

Applicant's intention (Paper 28) to provide a terminal disclaimer is acknowledged.

Claim Rejections - 35 USC § 112

5. Claims 165 and 166 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). In claims 165 and 166, glial cells are indicated as being "neuronal" whereas it is well established that glial cells are not neurons. It is suggested that the word "neural" be substituted for "neuronal"; support for this amendment is found in original claim 34.

6. Claims 123-166 stand rejected under 35 U.S.C. 112, first paragraph, as set forth previously in item 12 of Paper 36 and in item 13 of Paper 26, because the specification, while being enabling for methods of promoting growth, differentiation and/or survival of embryonic neuronal cells by administering a polypeptide (sonic hedgehog) of SEQ ID NO: 8, 11, 12, and 13 or an N-terminal autoproteolytic portion thereof (as described in the specification), does not reasonably provide enablement for administering a polypeptide other than a polypeptide of SEQ ID NO: 8, 11, 12, and 13, nor for the administration of portions of the polypeptides other than that of the N-terminal autoproteolytic portion, and nor does the specification provide enablement for promoting growth, differentiation and/or survival of neuronal cells other than embryonic cells. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the reasons of record.

Applicant argues that the specification clearly contemplates that hedgehog polypeptides can be used to influence not only the behavior of embryonic cells and tissues but also the behavior of adult cells. This argument has been fully considered but not deemed persuasive. The specification simply provides the speculation that adult cells would respond to hedgehog polypeptides (e.g. page 63, lines 12-32). The specification suggests/speculates that hedgehog polypeptides might be active in a multitude of neurologic systems and cell types (e.g. pages 63-66). In fact, most, if not all, aspects of neurobiology appear to be encompassed by the suggestions put forth in the specification. The highly skilled artisan would thus appreciate that the contemplations of the specification amount to no more than an invitation to begin a research plan to try to find areas of the adult nervous system that could be manipulated with hedgehog polypeptides, and then to try to find useful ways to manipulate such areas. The post-filing date references and Declarations, referred to by Applicant, are examples of the type extensive research and investigation that the specification has invited the artisan to perform. Thus, the skilled artisan would not be able to make and use the invention as claimed without the benefit of such post-filing date information. The invitation to perform such extensive research is not a substitute for such research.

Applicant provides a multitude of examples wherein one species of sonic hedgehog protein is effective in another species (pg 14), and concludes (pg 15) that hedgehog signaling is

tolerant to some variation in the sequence of the hedgehog protein. This argument has been fully considered but not deemed persuasive. First, Applicant is reminded that the claims have been indicated to be enabled for sonic hedgehog from each of the disclosed species (see above). Second, regarding the concept of signaling being tolerant to sequence variation, there is variation between the naturally occurring sonic hedgehog proteins, referred to in Applicant's examples; yet this variation has occurred under the constraint of over 100 million years of selective pressure during the evolution of these species. These differences have arisen through random mutation, and those that did not function have been eliminated. The specification has provided little more than this strategy of evolution to guide the artisan in the construction of mutants that will function as required. The artisan is simply invited to embark on an essentially random trial and error process of experimentation wherein in amino acids are substituted/added/deleted from the parent sequence and then assayed for activity to try to find variants that work. Third, the claims stipulate that the protein be required to have some effect on neuronal cells, and the specification has not provided a rapid assay such that the artisan would expected that screening for variants would be routine. Fourth, the task of assaying the mutants for function is complicated by the fact that the specification has failed to teach exactly what function should be expected in adult tissues. Thus, the extensive experimentation required to make and test the genus of mutants encompassed by the claims is unduly burdensome.

Applicant's arguments regarding the number of inoperable embodiments that are allowed to be in a claim are unpersuasive because the issue is that the specification has failed to teach how to make operable embodiments without undue experimentation.

Applicant argues that because of the suggestions provided in the specification regarding hedgehog proteins and known disorders, the skilled artisan would be motivated to practice the invention. Applicant also asserts that the examiner has based the rejection on the argument that "one of skill in the art would not be motivated to experiment on adult neuronal cells based on Applicant disclosure" see page 16 of Paper 45. However, the examiner can find no mention of such an argument. To the contrary, it is agreed that the skilled artisan would be motivated to look for effects of hedgehog proteins in the adult, as is evidenced by the tremendous volume of post-filing date research on the subject. However, the issue is that an invitation to perform this research is not a substitute for the facts that come from such research, e.g. what cell types are amenable to manipulation, which are not, and how, in particular, can an individual cell-type be manipulated. While it may be routine in the art of scientific investigation to begin to answer these types of questions, an invitation to begin the quest, does not provide enablement.

Applicant's arguments regarding the expression of patched have been substantially addressed previously. As set forth previously, the specification discloses experiments that indicate sonic hedgehog is not expressed in adult tissues (see page 110, lines 10-11). One of skill in the art would therefore expect that adult tissues would not be responsive to sonic hedgehog in the same way that embryonic tissues are, or perhaps not responsive at all. The specification has

provided no guidance as to the nature of the response of adult tissues to sonic hedgehog. Additionally, Applicant admits that the specification does not provide any information about patched expression in the adult either. Applicant, provides a pre-filing date reference (Takabatake et al., FEBS Letts 410(485-489)1997) that indicates that Shh and patched are expressed in adult neural ocular tissues and other adult tissues. Takabatake et al., merely speculate that "judging from their roles in embryos, hh molecules might function in certain cell-cell communications between deferent types of tissues in the adult eye" (see col 1 of page 489).

Applicant argues that lack of expression of the protein in the adult would not be construed by the artisan as evidence that the protein would not be useful, and that many compounds that are not endogenously expressed are known to be useful. The examiner agrees in part, as stated above, the skilled artisan would be motivated to look for effects of hedgehog proteins in the adult, as is evidenced by the post-filing date research on the subject. However an invitation to perform that research does not constitute an enabling disclosure to use the polypeptides in any particular way in adult tissues.

Applicant argues that the concept of using embryonically derived proteins as, *inter alia*, trophic factors in adult tissues is well established in the art, and that at the time of filing, one of skill in the art would appreciate that signaling molecules that are expressed in embryonic tissues are also used in the adult. This argument has been fully considered but not deemed persuasive. The particular neurotrophin family members that are the subject of Applicant's cited references are completely unrelated, structurally and functionally, to hedgehog proteins. Further,

neurotrophins are known to be important both during development and in the adult as trophic factors for neurons - as is well established in the art. Additionally, the state of the art of hedgehog signaling in adult tissues, at the time of filing, was extraordinarily primitive compared to that of the neurotrophins. Triffort et al., Journal of Neurochemistry 70(1327-1330)1998, describe the state of the art as follows: "The roles of HH signaling in adult vertebrates have been poorly documented so far, particularly in the brain where Ptc and Smo transcripts have been identified", see the last paragraph of col 1 of page 1327. Thus, even if it is agreed that the artisan would be motivated to look for effects of hedgehog proteins in the adult nervous system, the artisan would be required to perform extensive research and investigation to determine what cell types were amenable to manipulation with sonic hedgehog. Further, Miao et al., J. Neuroscience, 17(15)5891-5899, 1997 state that "there is no direct correlation between the neuron phenotypes induced by Shh and those supported by Shh in a trophic manner", see col 1 of page 5898. Thus, the particular teachings in the specification regarding embryonic expression of hedgehog and manipulation of embryonic tissues could not be expected to provide the artisan with the knowledge required to manipulate adult tissues.

Conclusion

No claims are allowable.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Fridays from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

February 23, 2003

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
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